

CANADA

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Production of Bactericidal Compositions

Henry J. Ferlin and Joseph V. Karabinos, Joliet, Illinois, U.S.A., assignors, by means assignments, to Olin Mathieson Chemical Corporation, New York, New York, U.S.A.

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19 Claims

The present invention relates to compositions having or leading to bactericidal properties in a wide variety of usages. In particular, it relates to a combination of ingredients which is capable of bactericidal action in the presence of moisture or water, at high dilutions of the principal active ingredient.

Ordinary household soap has long been known to be effective as a germicidal agent, it being commonly an alkali metal soap of fatty acids having from 16 to 18 carbon atoms. Such soap has a pH over 7. The fatty acids involved in such soap are, in their free state, insoluble in water and are not known to exist in water solution at pH values below 7.

The present invention is based upon the discovery that saturated aliphatic monocarboxylic acids having from 9 to 12 carbon-atom chains, when in water solution at pH values in the approximate range from 3 to 6 are powerful bactericides at great dilutions thereof, yet are not harmful to many common materials nor to the human skin and mucous membranes.

It is the general object of the present invention to provide a bactericidal composition involving as the active ingredient saturated aliphatic monocarboxylic acid having from 9 to 12 carbon-atom chains and a pH-lowering agent to provide and maintain a pH in the approximate range from 3 to 6 whereby in or in contact with an aqueous medium the composition is highly effective at great dilution.

Various other and ancillary objects and advantages of the present invention will become apparent from the following description and explanation of the invention given in connection with the accompanying drawing in which:

Fig. 1 is a plot of highest killing dilution against pH for aqueous solutions containing the subject acids, and Fig. 2 is a second plot of the same data, showing the highest killing dilution against the carbon-chain length of the acids.

The present invention involves numerous types of compositions containing a combination of one or more of the subject saturated aliphatic monocarboxylic acids and a pH-lowering agent which is capable of effecting and maintaining in the presence of water and in use of the combination a pH in the approximate range from 3 to 6, when such composition is present with water or moisture for

bactericidal use. The composition may include water, or be anhydrous, or have an aqueous solution ranging from zero to that of an aqueous solution.

For practical purposes aqueous bactericidal solutions of the preferred character are those which have killing power at very high dilutions in water. Their comparative potencies are reported in terms of "highest killing dilution" under specified or standard conditions including specified bacteria and exposure times. Such a procedure is given hereinafter as Test A by which some of the data hereof have been prepared. In consequence, a satisfactory bactericide must retain its killing power on dilution up to some arbitrary value.

Compositions having a pH lower than approximately pH 3 are by virtue of that pH generally bactericidal in character regardless of the ingredients. At pH of about 3 and higher a bactericidal agent must be present in quantity to exert bactericidal action. Consequently, a pH of approximately 3 is herein considered to be the lower limit for the present invention. The upper limit is somewhere between pH of 6 and 7, and variable with the particular acid, but for the generic group, a pH of approximately 6 is herein considered to be the upper limit.

In developing the present invention it has been ascertained that a lower pH in the approximate range from 3 to 6 is more favorable than a higher one. Consequently, an agent is used which effects and maintains a favorable pH, especially as dilution increases. Such agent is broadly referred to herein as a pH-lowering agent because it lowers the pH due to the subject acid alone. It has been found that a solution in which the solute consists of a subject acid in its free state has a pH which is elevated on dilution. The preferred pH-lowering agent is a pH-buffer, used for its effectiveness to prevent an adverse change in pH on dilution and adverse change by contact with reactive material sometimes encountered in use of bactericides. A buffer salt may be used to effect and maintain a desired pH for conditions of use wherein the composition may be exposed to material tending to react with the composition and thereby change the pH.

Among the pH-lowering agents which are used with the free subject acid in the combination of the present invention are: acetic, citric, tartaric, oxalic, boric, hydrochloric, sulfuric and phosphoric

acids, sodium acetate with acetic acid, sodium citrate with citric acid, monosodium or monopotassium acid phosphate. Some of these agents act as buffers. The most effective agents are weak acids, such as boric and organic acids, and salts of a strong tribasic inorganic acid such as phosphoric acid, which salts present a pH in the desired range. The phosphate radical, although effective in a pH-lowering agent, is less desired than others because it is a nutrient for bacteria.

The subject acids of the present invention are stated in the literature to have solubilities as follows:

TABLE I

| Acid | Solubility gm. per 100 gm. H ₂ O | Dilution 1 to - |
|-----------------|--|--------------------|
| Pelargonic..... | 0.026 | 1,260 |
| Capric..... | 0.018 | 5,600 |
| Undecylic..... | 0.0025 | 10,750 |
| Lauric..... | 0.0044 | 18,200 |

In testing the above subject acids attempts were made to form saturated solutions in water by shaking the solid free acid in water for two hours. The resulting solutions are herein referred to as supposedly saturated solutions, and as having supposed dilutions, but this is only for the purpose of aiding the explanation of the invention. It is believed from the experience obtained in other ways of effecting solution that the supposedly saturated solutions were not in fact such, and that they exist in fact at greater dilutions than the indicated supposed dilutions.

Table II shows the pH values of certain solutions of supposed dilutions and the bactericidal activity thereof in 5, 10 and 15 minutes by the standard Test A. Solutions A, B, C, and D are the supposedly saturated solutions of the four subject acids showing only pelargonic acid to be effective. When these supposedly saturated solutions are diluted with an equal volume of water to form solutions E to H, they have elevated pH values, and they are ineffective as bactericides by Test A. Solutions A to D and E to H, when adjusted to pH 3 with acetic acid, provide solutions I to P. Of these, solutions I to J at supposed saturation and at pH of 3 are effective in Test A. The pH adjustment has rendered the solutions B, C and D bactericidal.

TABLE II

| Supposedly Saturated Solutions | pH | Minutes of Exposure | | | Supposed Dilution |
|---|-----|---------------------|----|----|-------------------|
| | | 5 | 10 | 15 | |
| A Pelargonic Acid..... | 3.7 | + | + | + | 1 to 1,260 |
| B Capric Acid..... | 4.0 | + | + | + | 1 to 5,600 |
| C Undecylic Acid..... | 4.4 | + | + | + | 1 to 10,750 |
| D Lauric Acid..... | 5.0 | + | + | + | 1 to 18,200 |
| Solutions A to D Diluted With 1 Volume H ₂ O | | | | | |
| E Diluted Solution A..... | 4.0 | + | + | + | 1 to 7,700 |
| F Diluted Solution B..... | 4.3 | + | + | + | 1 to 13,320 |
| G Diluted Solution C..... | 4.6 | + | + | + | 1 to 21,550 |
| H Diluted Solution D..... | 5.1 | + | + | + | 1 to 36,400 |
| Solutions A to D at pH 3 With Acetic Acid | | | | | |
| I Adjusted Solution A..... | 3.0 | + | + | + | 1 to 1,260 |
| J Adjusted Solution B..... | 3.0 | + | + | + | 1 to 5,600 |
| K Adjusted Solution C..... | 3.0 | + | + | + | 1 to 10,750 |
| L Adjusted Solution D..... | 3.0 | + | + | + | 1 to 18,200 |
| Solutions E to H at pH 3 With Acetic Acid | | | | | |
| M Adjusted Solution E..... | 3.0 | + | + | + | 1 to 7,700 |

| | | | | |
|----------------------------|---|---|---|-------------|
| N Adjusted Solution F..... | + | + | + | 1 to 13,320 |
| O Adjusted Solution G..... | + | + | + | 1 to 21,550 |
| P Adjusted Solution H..... | + | + | + | 1 to 36,400 |

Solution A Diluted With 1 Volume H₂O

| | | | | |
|--|---|---|---|-------------|
| Q - And Adjusted to pH 3 With Acetic Acid..... | + | + | + | 1 to 11,550 |
|--|---|---|---|-------------|

0 = No Growth + = Growth

In the case of pelargonic acid solution M at half of supposed-saturation and at pH of 3, the bactericidal activity is brought about by the pH adjustment of solution E. But this does not follow with capric acid and undecylic acid solutions N and O, and it follows only in part with lauric acid solution P. In the 5-minute exposure, the lauric acid was not bactericidal in Test A but was found so to be in the 10- and 15-minute exposure.

Dilution of pelargonic acid solution A with two volumes of water and adjustment of its pH to 3 with acetic acid to provide solution Q were ineffective steps to retain bactericidal value by Test A.

The data in Table II are to establish trends, and because of uncertainty of concentration as absolute values, they may not be relied upon. More precise data is available by more certain ways to effect dissolution or homogeneous dispersion in water of the subject acids.

One of the ways to effect definite concentrations of a subject acid is to neutralize the free acid with sodium hydroxide to form the sodium salt thereof, which is readily soluble in water. Then a pH-lowering acid, such as acetic acid, is added to adjust the pH value to a desired value in the approximate range from 3 to 6 at the dilution to be tested for bactericidal activity. The amount of acid needed increases as the pH is lowered in said range. By this method a known amount of subject acid is dispersed or dissolved in aqueous solution in the presence of the resulting sodium salt of the added acid which is also effective as a part of the total buffering content. In carrying out the above procedure for test purposes, one gram of each subject acid was dissolved in a sufficient quantity of a normal solution of sodium hydroxide (40 grams per liter) to neutralize the acid, excess being permissible in view of subsequent addition of acid. Then the solution was diluted with sterile water to 500 ml. as a stock solution. The stock solutions were diluted to predetermined values and then adjusted to the desired pH by careful addition of acetic acid. The resulting sodium acetate, of course in small amount, is an effective buffer salt. Solutions prepared in this way were subjected for comparison to Test A, using the 10-minute exposure thereof with respect to *Staphylococcus aureus*, also known as *Micrococcus pyogenes* var. *aureus* (FDA Strain 209 P). The lowest dilution for positive growth of the test bacteria is reported herein as L-P, and also the highest dilution for negative growth is reported herein as H-N, as presented in Tables III and IV.

TABLE III

| Acid | Highest Dilution for Negative Growth after Ten-Minute Exposure (H-N) | | | |
|-----------------|--|-------------|-------------|-------------|
| | pH 3 | pH 4 | pH 5 | pH 6 |
| Pelargonic..... | 1 to 12,000 | 1 to 11,000 | 1 to 7,000 | 1 to 500 |
| Capric..... | 1 to 25,000 | 1 to 11,000 | 1 to 17,000 | 1 to 11,000 |
| Undecylic..... | 1 to 25,000 | 1 to 11,000 | 1 to 25,000 | 1 to 25,000 |
| Lauric..... | 1 to 25,000 | 1 to 18,000 | 1 to 2,000 | 1 to 500 |

TABLE IV

| Lowest Dilution for Positive Growth after Ten-Minute Exposure (L-P) | | | | |
|---|-------------|-------------|-------------|-------------|
| Acid | pH 3 | pH 4 | pH 5 | pH 6 |
| Pelargonic..... | 1 to 15,000 | 1 to 12,000 | 1 to 8,000 | 1 to 1,000 |
| Capric..... | 1 to 80,000 | 1 to 80,000 | 1 to 10,000 | 1 to 10,000 |
| Undecylic..... | 1 to 80,000 | 1 to 80,000 | 1 to 17,000 | 1 to 11,000 |
| Lauric..... | 1 to 80,000 | 1 to 11,000 | 1 to 4,000 | 1 to 500 |

Fig. 1 is a plot from data of Table III of the values H-N vertically against pH horizontally. Curves 9 through 12 are numbered according to the number of carbon atoms in the acid. These show in each case that as the pH is lowered the highest dilution for killing (H-N) is increased. Undecylic acid is the most potent over the entire pH range. The plotted limits found are not inconsistent with the possibility that the supposed saturated solutions of Table II are not as concentrated as the supposed saturated values of the literature. The data of Table IV shows that the data of Table III is near the absolute limit without being necessarily absolute.

Fig. 2 is a second plot of data from Table III corresponding to the data in Fig. 1, but plotting H-N against carbon-chain lengths of the subject acids for the same pH values. These show the highest peak for undecylic acid which is thereby evidenced as the most potent and hence preferred.

Further to demonstrate the property of undecylic acid, the values H-N and L-P were determined for 10-minute exposures to other bacteria using solutions prepared as for Tables III and IV. Table V shows the values. The organisms were chosen to give representative ones of gram-positive and gram-negative types, as well as pathogenic and common food contaminants, not only bacteria but also yeasts.

TABLE V

| Organism | H-N | L-P |
|---|--------------|--------------|
| <i>Escherichia coli</i> (W. C. Morse AM508 STRAIN 191)..... | 1 to 85,000 | 1 to 85,000 |
| <i>Salmonella paratyphi</i> | 1 to 80,000 | 1 to 100,000 |
| <i>Shigella flexner</i> | 1 to 85,000 | 1 to 80,000 |
| <i>Serratia marcescens</i> | 1 to 85,000 | 1 to 80,000 |
| <i>Sarcina lutea</i> | 1 to 100,000 | 1 to 100,000 |
| <i>Enterobacter aerogenes</i> | 1 to 100,000 | — |
| <i>Bacillus subtilis</i> | 1 to 100,000 | — |
| <i>Aspergillus fumigatus</i> | 1 to 100,000 | — |

The foregoing establishes that the potency may vary with different bacteria. By other tests it has been determined that a dilution of 1 to 180,000 parts of undecylic acid at pH of 3 with acetic acid and sodium acetate (resulting from the dissolution procedure described above) is effective on *Bacillus stearothermophilus* in an exposure of 10 minutes.

It is not necessary to adjust the pH with acetic acid in employing the stock solution of the sodium salt. In the case of undecylic acid several acids were compared in tests as conducted for Tables III and IV with *Staphylococcus aureus* at pH 3, allowing 48 hours for incubation after exposures of 5, 10 and 15 minutes. These results reported in Table VI are the same for each exposure.

TABLE VI

| Undecylic Acid | | |
|----------------|-------------|-------------|
| Adjusting Acid | H-N | L-P |
| Acetic..... | 1 to 80,000 | 1 to 80,000 |
| Chloric..... | 1 to 80,000 | 1 to 80,000 |
| Oxalic..... | 1 to 80,000 | 1 to 80,000 |

| | | |
|-------------------|-------------|-------------|
| Boric..... | 1 to 80,000 | 1 to 80,000 |
| Phosphoric..... | 1 to 80,000 | 1 to 80,000 |
| Hydrochloric..... | 1 to 80,000 | 1 to 80,000 |

In all of these tests the activities of the bacteria were checked daily against a phenol solution, the highest killing dilution of which in 10 minutes was of the order of 1 to 120. Within the limits prescribed for the present invention the compositions are far superior to phenol, it being noted that this corresponds to a dilution of about 4 phenol to 500, whereas in the poorest showing herein, with lauric acid at pH of 6, the H-N value is about 1 to 500±50.

Since the tests above reported were conducted with solutions containing the sodium ion as a result of the method of preparing the solution, it has been determined that the sodium ion is not of itself the cause of the activity. Preparations without the sodium ion have been made.

One type of such preparation without the sodium ion involves ethyl alcohol at various aquesities as the vehicular liquid for various dilutions of undecylic acid and at various pH values. Using *Staphylococcus aureus* as the test bacteria and 5-, 10- and 15-minute exposures, various dilutions were found to be bactericidal as reported in Table VII.

TABLE VII

| Killing Dilutions in Aqueous Alcohol Solutions (% by Volume) | | | | |
|--|--------------|-----|-----|-----|
| pH | 2% | 50% | 75% | 90% |
| 3 | 1 to 80,000 | | | |
| 4 | 1 to 40,000 | | | |
| 5 | 1 to 8,000 | | | |
| | 1 to 10,000 | | | |
| | 1 to 100,000 | | | |

Another method of eliminating sodium or like ion and of making a useful composition containing the combination of the present invention is to form an anhydrous mass, using an inert base such as petroleum jelly, mineral oil, lanolin, fatty acid glycerides, or wax such as carnauba. The subject acid readily dissolves in such bases. Acetic acid preferably as its non-aqueous glacial form is incorporated in amount such that on exposure of the composition to aqueous media, it imparts a pH in the approximate range from 3 to 6. Ointments for application to the skin are thus formed. Test B as given below is standard for testing such bactericidal ointments and is the test by which the present invention in this respect has been tested. Wax compositions may be made including the combination of the present invention. Compositions having such non-aqueous vehicles may be emulsified in a manner to present to the aqueous phase the pH value of the composition.

Ointments

From use of Test B (described below) there are reported results in terms of width in millimeters of a band around the blotter disk, the wider the band the more effective the composition. Each composition is reported as a rating and by band width.

Ointments designated X, Y, and Z of the present invention were made containing by weight 95 to 92 percent of petroleum jelly, 5 percent of undecylic acid and, respectively, 1, 2 or 3 percent of glacial acetic acid. Controls were also made and tested using the compositions set forth in Table VIII.

TABLE VIII

| Used per 100 Parts of Petroleum Jelly Fine Additive | | | |
|---|-----|----------------|--------------|
| Control | pH | % Additive | For Ointment |
| 1 | — | 0 phenol..... | X, Y, Z |
| 2 | 4.4 | 1 acetic..... | X |
| 3 | 4.9 | 1 acetic..... | Y |
| 4 | 5.8 | 1 undecylic... | Z, Y, Z |

The ointments and controls subjected to Test B gave results as given below in Table IX.

TABLE IX—TEST B

| Composition | pH* | Inhibition | Blotter Band Width |
|-------------|-----|------------|--------------------|
| 1 | — | Good | 9 mm. |
| 2 | 4.4 | Very Good | 7 mm. |
| 3 | 4.9 | Excellent | 7 mm. |
| 4 | — | Negative | — |
| 5 | 4.4 | Poor | 1 mm. |
| 6 | 4.9 | Very Poor | 7 mm. |
| 7 | 5.8 | Poor | 1 mm. |
| 8 | 5.8 | Poor | 1 mm. |
| 9 | 5.8 | Fair | 1.5 mm. |

*Determined on emulsion with equal part of water.

In Table IX above it is apparent that the addition of acetic acid to composition 1, forming the ointments X, Y and Z greatly increased the bactericidal quality of the ointment. Ointment Z and control 6 have the same content of acetic acid, and the great difference in bactericidal value is due to the presence of the undecylic acid.

It is noted that composition Z has a pH of 5.8. Different methods of determination, or errors in observation, may readily lead to results varying at least 0.1 in pH. The expression "approximate range from 5 to 6" comprehends pH of 5.9 ± 1 as given for Z in Table IX, and also 6 ± 0.3 so that the said range is 5 to 6 ± 0.3 .

Experiments conducted at pH of 7 with lauric acid containing sodium laurate gave results with *Escherichia coli* not much better than phenol as the bactericide. Consequently, pH at 6 ± 0.3 is taken as the upper limit.

By Test B lanolin and hydrogenated cottonseed oil (commercial trade-mark "Crisco") were studied on *Staphylococcus aureus*, and the results are given in Table X as in Table IX for petroleum jelly.

TABLE X—TEST B

| Staphylococcus aureus | | | |
|-------------------------------|--------|-----------------|------------------------|
| Composition (Parts by Weight) | | | |
| Vehicle | Acetic | Subject | Blotter Band Width |
| 100 Lanolin..... | 3 | 5 polargenic... | 2.4 Very Good. 4.0 mm. |
| 100 Lanolin..... | 3 | 5 lauric..... | 3.7 Fair..... 1.5 mm. |
| 100 Crisco..... | 3 | 5 polargenic... | 3.5 Very Good. 3.6 mm. |
| 100 Crisco..... | 3 | 5 lauric..... | 4.8 Very Good. 3. mm. |

*Determined on emulsion with equal part of water.

The values given are not absolute values for a given composition. The kind of bacteria used in

Test B affects the comparison. Table XI shows Test B carried out on *Escherichia coli*.

TABLE XI—TEST B

| Composition (Parts by Weight) | | | |
|-------------------------------|--------|-----------------|--------------------|
| Vehicle | Acetic | Subject | Blotter Band Width |
| 100 Petroleum Jelly..... | 0 | 0..... | 0 |
| 97 Petroleum Jelly..... | 3 | 0..... | 0 |
| 94 Petroleum Jelly..... | 6 | 0 phenol..... | 1 mm. |
| 95 Petroleum Jelly..... | 0 | 5 polargenic... | 0 |
| 92 Petroleum Jelly..... | 0 | 5 polargenic... | 0.5 mm. |
| 94 Petroleum Jelly..... | 0 | 5 undecylic... | 0 |
| 93 Petroleum Jelly..... | 3 | 5 undecylic... | 1 mm. |
| 94 Petroleum Jelly..... | 0 | 5 lauric..... | 0 |
| 95 Petroleum Jelly..... | 1 | 5 lauric..... | 0 |

The last item is an exception as a bactericidal in the case of the particular bacteria.

The relative efficiency of bactericides and disinfectants is determined by testing their ability to kill a test organism and comparing the result with that of phenol under the same conditions. The "phenol coefficient" is the ratio of the greatest killing dilution (G.K.D.) of the subject composition to that of phenol, in 10 minutes but not in 5 minutes of exposure. In the present invention the phenol coefficients are so high that the results are reported in the values H-N.

Test A

This test was devised by the U.S. Public Health Service (see Bryan and Bryan, "Principles and Practice of Bacteriology", published by Barnes and Noble, Inc., Edition 4, 1931, p. 86).

It is conducted as follows:

1. Make dilutions of 1 part of phenol in 80, 90, 100, 110, 120, and 130 parts of water and place 5 ml. in test tubes in a water bath at 20°C. for at least five minutes.
2. Make various test dilutions of the subject composition, and place 5 ml. in test tubes in a water bath at 20°C. for at least 5 minutes.
3. To the phenol and subject dilutions add a quantity in the range from 0.1 to 0.5 ml. of a culture of the selected bacteria, and expose for 5, 10 and 15 minutes.
4. Transfer a loopful to sub-culture tubes containing nutrient agar.
5. Incubate for 48 hours at 37°C.
6. Record growth (+) or not growth (—) or (O).

Test B

Test B is described on pages 87-88 of the reference for Test A.

It is briefly as follows:

1. Seed nutrient agar in its liquid state at 42° to 45°C. with a 24-hour broth culture of *Staphylococcus aureus*.
2. Pour into a sterile Petri dish and allow to harden.
3. Place test composition in intimate contact with the agar.
- 3(a). Soak test composition into a 20 mm. diameter blotter disk, and place disk on agar.
4. Incubate under unglazed porcelain top at 37°C. for 48 hours.
5. Observe presence or absence of a clear zone around contact area.

5(a). Width of zone around disk is determined for comparison records.

From the foregoing it is to be understood that the composition of the invention may be embodied in a wide variety of compositions falling within the scope of the appended claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

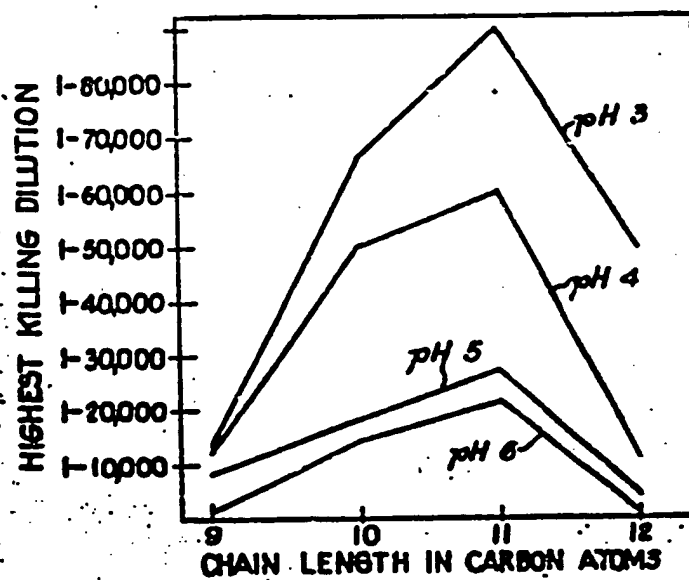
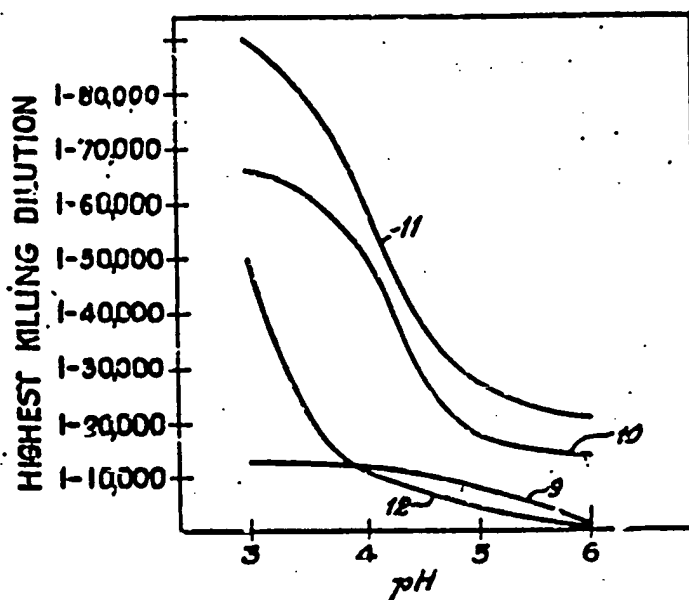
1. An aqueous bactericidal composition comprising in from 500 to 88,000 parts of water one part of an acid selected from the group consisting of pelargonic, capric, undecylic and lauric acids, and a small quantity of water-soluble acid having a greater dissociation constant than the selected acid, the composition having a pH in the range from 3 to 6.
2. A composition according to claim 1 in which the said water-soluble acid is acetic acid.
3. A composition according to claim 1 in which there is also present an inorganic salt of said water-soluble acid which is the reaction product of a water-soluble inorganic soap of said one part of selected acid and said water-soluble acid.
4. A composition according to claim 3 in which the salt is an alkali-metal salt.
5. A composition according to claim 3 in which the water-soluble acid is acetic acid.
6. A composition according to claim 3 in which the water-soluble acid is acetic acid and the salt is alkali-metal acetate.
7. An aqueous bactericidal composition comprising in from 500 to 88,000 parts of water one part of undecylic acid, and a small quantity of water-

soluble acid having a greater dissociation constant than undecylic acid, said composition having a pH in the range from 3 to 6.

8. A composition according to claim 7 in which the water-soluble acid is acetic acid.
9. A composition according to claim 7 in which there is also present an inorganic salt of said water-soluble acid which is the reaction product of a water-soluble inorganic soap of said one part of undecylic acid and said water-soluble acid.
10. A composition according to claim 9 in which the salt is an alkali-metal salt.
11. A composition according to claim 9 in which the water-soluble acid is acetic acid.
12. A composition according to claim 9 in which the water-soluble acid is acetic acid and the salt is alkali-metal acetate.
13. A bactericidal composition characterized by a pH in water in the range from 3 to 6 and comprising an acid selected from the group consisting of pelargonic, capric, undecylic and lauric acids, and a water-soluble acid having a greater dissociation constant than that of said selected acid.

W. B. JONES,
38 South Dearborn St.,
Chicago, Ill.

FETHERSTONHAUGH & CO.,
600 University Ave.,
Toronto, Ont.,
Patent Agents of the Applicants.



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